General

Guideline Title

2012 American College of Rheumatology guidelines for management of gout. Part 2: therapy and antiinflammatory prophylaxis of acute gouty arthritis.

Bibliographic Source(s)

Khanna D, Khanna PP, Fitzgerald JD, Singh MK, Bae S, Neogi T, Pillinger MH, Merill J, Lee S, Prakash S, Kaldas M, Gogia M, Perez-Ruiz F, Taylor W, Liote F, Choi H, Singh JA, Dalbeth N, Kaplan S, Niyyar V, Jones D, Yarows SA, Roessler B, Kerr G, King C, Levy G, Furst DE, Edwards NL, Mandell B, Schumacher HR, Robbins M, Wenger N, Terkeltaub R. 2012 American College of Rheumatology guidelines for management of gout. Part 2: therapy and antiinflammatory prophylaxis of acute gouty arthritis. Arthritis Care Res (Hoboken). 2012 Oct;64(10):1447-61. [68 references] PubMed

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

Note from the National Guideline Clearinghouse (NGC): This article concentrates on two of the four gout domains that the American College of Rheumatology (ACR) requested for evaluation of pharmacologic and nonpharmacologic management approaches: analgesic and antiinflammatory management of acute attacks of gouty arthritis and pharmacologic antiinflammatory prophylaxis of acute attacks of gouty arthritis. Part 1 of the guidelines focused on systematic nonpharmacologic measures (patient education, diet and lifestyle choices, identification and management of comorbidities) that impact hyperuricemia, and made recommendations on pharmacologic urate-lowering therapy (ULT) in a range of case scenarios of patients with disease activity manifested by acute and chronic forms of gouty arthritis, including chronic tophaceous gouty arthropathy (see the NGC summary of the ACR guideline 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia).

The levels of evidence supporting the recommendations (A-C) are defined at the end of the "Major Recommendations" field.

Recommendations for Pharmacologic Therapy for Attacks of Acute Gout

General Principles for Treatment of the Acute Attack of Gouty Arthritis ("Acute Gout" Management)

Figure 2 in the original guideline document summarizes the overall recommendations on treatment of an acute gouty arthritis attack. The Task Force Panel (TFP) recommended that an acute gouty arthritis attack should be treated with pharmacologic therapy (evidence C), and that treatment should be preferentially initiated within 24 hours of onset of an acute gout attack (evidence C). The latter recommendation was based on

consensus that early treatment leads to better patient-reported outcomes. The TFP also recommended continuing established pharmacologic ULT without interruption during an acute attack of gout (evidence C), i.e., do not stop ULT therapy during an acute attack. The TFP also recommended patient education, not simply on dietary and other triggers of acute gout attacks, but also providing the patients with instruction so that they can initiate treatment upon signs and symptoms of an acute gout attack, without the need to consult their health care practitioner for each attack (evidence B). Moreover, fundamental patient education includes discussion that gout is caused by body excess of uric acid, and that only effective ULT is potentially "curative" (evidence B).

Initial Pharmacologic Treatment of the Acute Attack of Gouty Arthritis

The TFP recommended that the choice of pharmacologic agent should be based upon severity of pain and the number of joints involved (see Figure 2 in the original guideline document). For attacks of mild/moderate gout severity (≤6 of 10 on a 0–10 pain visual analog scale [VAS]) particularly those involving 1 or a few small joints or 1 or 2 large joints, the TFP recommended that initiating monotherapy was appropriate, with recommended options being oral nonsteroidal antiinflammatory drugs (NSAIDs), systemic corticosteroids, or oral colchicine (evidence A for all therapeutic categories) (see Figure 2 in the original guideline document). The TFP also voted that combination therapy was an appropriate option to consider when the acute gout attack was characterized by severe pain, particularly in an acute polyarticular gout attack or an attack involving 1–2 large joints (evidence C) (see Figure 2 in the original guideline document). The TFP did not rank one therapeutic class over another. Therefore, it is at the discretion of the prescribing physicians to choose the most appropriate monotherapy based on the patient's preference, prior response to pharmacologic therapy for an acute gout attack, and associated comorbidities. Recommendations for appropriate combination therapy options are highlighted in Table 1 in the original guideline document and discussed below. The TFP did not vote on case scenarios for specific renal or hepatic function impairment–adjusted dosing and individual contraindications or drug–drug interactions with pharmacologic therapies.

NSAIDs

For NSAIDs, the TFP recommended full dosing at either the Food and Drug Administration (FDA)– or European Medical Agency–approved antiinflammatory/analgesic doses used for the treatment of acute pain and/or treatment of acute gout (evidence A–C) (see Figure 3A in the original guideline document). The FDA has approved naproxen (evidence A), indomethacin (evidence A), and sulindac (evidence B) for the treatment of acute gout. However, analgesic and antiinflammatory doses of other NSAIDs may be as effective (evidence B and C). For cyclooxygenase 2 (COX-2) inhibitors, as an option in patients with gastrointestinal contraindications or intolerance to NSAIDs, published randomized controlled trials support the efficacy of etoricoxib (evidence A) and lumiracoxib (evidence B), but these agents are not available in the U.S., and lumiracoxib has been withdrawn from use in several countries due to hepatotoxicity. A randomized controlled trial of a single comparison of celecoxib versus indomethacin suggested effectiveness of a high-dose celecoxib regimen (800 mg once, followed by 400 mg on day 1, then 400 mg twice daily for a week) in acute gout. The TFP recommended this celecoxib regimen as an option for acute gout in carefully selected patients with contraindications or intolerance to NSAIDs (evidence B), keeping in mind that the risk/benefit ratio is not yet clear for celecoxib in acute gout.

The TFP did not reach a consensus to preferentially recommend any one specific NSAID as first-line treatment. The TFP did recommend continuing the initial NSAID inhibitor treatment regimen at the full dose (if appropriate) until the acute gouty attack completely resolved (evidence C). The option to taper the dose in patients with multiple comorbidities/hepatic or renal impairment was reinforced by the TFP, without specific TFP voting or more prescriptive guidance. Last, there was no TFP consensus on the use of intramuscular ketorolac or topical NSAIDs for the treatment of acute gout.

Colchicine

The TFP recommended oral colchicine as one of the appropriate primary modality options to treat acute gout, but only for gout attacks where the onset was no greater than 36 hours prior to treatment initiation (evidence C) (see Figure 3B in the original guideline document). The TFP recommended that acute gout can be treated with a loading dose of 1.2 mg of colchicine followed by 0.6 mg 1 hour later (evidence B), and this regimen can then be followed by gout attack prophylaxis dosing 0.6 mg once or twice daily (unless dose adjustment is required) 12 hours later, until the gout attack resolves (evidence C). For countries where 1.0 mg or 0.5 mg rather than 0.6 mg tablets of colchicine are available, the TFP recommended, as appropriate, 1.0 mg colchicine as the loading dose, followed by 0.5 mg 1 hour later, and then followed, as needed, after 12 hours, by continued colchicine (up to 0.5 mg 3 times daily) until the acute attack resolves (evidence C). In doing so, the TFP rationale was informed by pharmacokinetics of the low-dose colchicine regimen, where the exposure to the drug in plasma becomes markedly reduced approximately 12 hours after administration in healthy volunteers. The TFP also evaluated prior European League Against Rheumatism (EULAR) recommendations on a colchicine dosing regimen for acute gout (0.5 mg 3 times daily) and the British Society for Rheumatology (BSR)-recommended maximum dosage for acute gout of 2 mg colchicine per day.

The algorithm in Figure 3B in the original guideline document outlines recommendations for colchicine based on FDA labeling and TFP deliberations and votes, including specific recommendations for patients already receiving colchicine acute gout attack prophylaxis. For more specific prescriptive guidance, practitioners should consult the FDA-approved drug labeling, including recommended dosing reduction in moderate

to severe chronic kidney disease (CKD), and colchicine dose reduction (or avoidance of colchicine use) with drug interactions with moderate to high potency inhibitors of cytochrome P450 3A4 and of P-glycoprotein; major colchicine drug interactions include those with clarithromycin, erythromycin, cyclosporine, and disulfiram. Last, the TFP did not vote on use of intravenous colchicine, since the formulation is no longer available in the U.S., due to misuse and associated severe toxicity.

Systemic and Intraarticular Corticosteroids and Adrenocorticotropic Hormone (ACTH)

When selecting corticosteroids as the initial therapy, the TFP recommended to first consider the number of joints with active arthritis. For involvement of 1 or 2 joints, the TFP recommended the use of oral corticosteroids (evidence B); the TFP additionally recommended the option of intraarticular corticosteroids for acute gout of 1 or 2 large joints (evidence B) (see Figure 3C in the original guideline document). For intraarticular corticosteroid therapy in acute gouty arthritis, it was recommended that dosing be based on the size of the involved joint(s), and that this modality could be used in combination (see Table 1 in the original guideline document) with oral corticosteroids, NSAIDs, or colchicine (evidence B). Specific doses for intraarticular corticosteroid therapy in specific joints were not considered during TFP voting.

Where intraarticular joint injection is impractical (e.g., polyarticular joint involvement, patient preference, or injection of the involved joint site is not in the scope of the provider's usual practice), the TFP recommended oral corticosteroids, prednisone, or prednisolone at a starting dosage of at least 0.5 mg/kg per day for 5–10 days, followed by discontinuation (evidence A), or alternately, 2–5 days at the full dose, followed by tapering for 7–10 days, and then discontinuation (evidence C). Acknowledging current prevalence of usage, the TFP recommended, as an appropriate option according to provider and patient preference, the use of an oral methylprednisolone dose pack for initial treatment of an acute attack of gout (evidence C).

The TFP also recommended, as appropriate in each case scenario, an alternative regimen of intramuscular single-dose (60 mg) triamcinolone acetonide, followed by oral prednisone or prednisolone (evidence C). However, there was no consensus by the TFP on the use of intramuscular triamcinolone acetonide as monotherapy. Last, the TFP vote also did not reach a consensus on use of ACTH (evidence A) for acute gout in patients able to take medications orally, but did consider ACTH in separate voting, as described below, for patients unable to take oral antiinflammatory medications.

Initial Combination Therapy for Acute Gout

For patients with severe acute gout attack (≥7 of 10 on a 0–10 pain VAS) and patients with an acute polyarthritis or involvement of more than 1 large joint, the TFP recommended, as an appropriate option, the initial simultaneous use of full doses (or, where appropriate, a full dose of one agent and prophylaxis dosing of the other) of two of the pharmacologic modalities recommended above. Specifically, the TFP recommended the option to use combinations of colchicine and NSAIDs, oral corticosteroids and colchicine, or intraarticular steroids with any of the other modalities (evidence C). The TFP was not asked by the Core Expert Panel (CEP) to vote on use of NSAIDs and systemic corticosteroids in combination, given CEP concerns about synergistic gastrointestinal tract toxicity of that drug combination.

Inadequate Response of an Acute Gout Attack to Initial Therapy

There is a lack of a uniform definition of an inadequate response to the initial pharmacologic therapy for an acute attack of gouty arthritis. Clinical trials in acute gout have defined variable primary end points for therapeutic response, such as percent improvement in pain on a Likert scale or VAS. To define inadequate response for scenarios in this section, the CEP asked the TFP to vote on various percent improvement definitions at time points such as 24, 48, or 72 hours. The TFP voted that the following criteria would define an inadequate response of acute gout to pharmacologic therapy in case scenarios: either <20% improvement in pain score within 24 hours or <50% improvement in pain score ≥24 hours after initiating pharmacologic therapy.

For the scenario of a patient with an acute attack of gouty arthritis not responding adequately to initial pharmacologic monotherapy, the TFP advised, without a specific vote, that alternative diagnoses to gout should be considered (see Figure 2 and Table 1 in the original guideline document). For patients not responding to initial therapy, the TFP also recommended switching to another monotherapy recommended above (evidence C) or adding a second recommended agent (evidence C). Use of a biologic interleukin-1 (IL-1) inhibitor (anakinra 100 mg subcutaneously daily for 3 consecutive days; evidence B) or canakinumab 150 mg subcutaneously as an option for severe attacks of acute gouty arthritis refractory to other agents was graded as evidence A in the systematic review. Given a lack of randomized studies for anakinra and the unclear risk/benefit ratio and lack of FDA approval for canakinumab at the time this was written, the authors, independent of TFP discussion, assessed the role of IL-1 inhibitor therapy in acute gout as uncertain.

Case Scenarios for the Nothing by Mouth (NPO) Patient

Acute gout attacks are common in the in-hospital setting, where patients may be NPO due to different surgical and medical conditions. In such a scenario, the TFP recommended intraarticular injection of corticosteroids for involvement of 1 or 2 joints (with the dose depending on the size of

the joint; evidence B) (see Figure 4 in the original guideline document). The TFP also recommended, as appropriate options, intravenous or intramuscular methylprednisolone at an initial dose at 0.5–2.0 mg/kg (evidence B).

The TFP also recommended, as an appropriate alternative for the NPO patient, subcutaneous synthetic ACTH at an initial dose of 25–40 IU (evidence A), with repeat doses as clinically indicated (for either ACTH or intravenous steroid regimens). There was no voting by the TFP on specific followup ACTH or an intravenous steroid dosing regimen, given a lack of evidence. In the scenario of the NPO patient with acute gout, there was no consensus on the use of intramuscular ketorolac or intramuscular triamcinolone acetonide monotherapy. Biologic IL-1 inhibition therapy remains an FDA-unapproved modality for NPO patients, without specific past evaluation in this population.

Critical Drug Therapy Adverse Event Considerations in Acute Gout

It was not possible to evaluate every permutation of gout treatment and comorbid disease, given the constraints of the project. The treating clinician will need to carefully weigh the complexities of each unique patient. TFP discussions emphasized that potential drug toxicities due to comorbidities and drug–drug interactions are considerable in treatment of acute gout. Some examples include underlying moderate and severe CKD (NSAIDs, COX-2 inhibitors, colchicine), congestive heart failure (NSAIDs, COX-2 inhibitors), peptic ulcer disease (NSAIDs, COX-2 inhibitors, corticosteroids), anticoagulation or antiplatelet aggregation therapy (NSAIDs), diabetes mellitus (corticosteroids), ongoing infection or high risk of infection (corticosteroids), and hepatic disease (NSAIDs, COX-2 inhibitors, colchicine).

Complementary Therapies for Acute Gout Attack

The TFP recommended topical ice application to be an appropriate adjunctive measure to one or more pharmacologic therapies for acute gouty arthritis (evidence B). The TFP voted, as inappropriate, the use of a variety of oral complementary agents for the treatment of an acute attack (cherry juice or extract, salicylate-rich willow bark extract, ginger, flaxseed, charcoal, strawberries, black currant, burdock, sour cream, olive oil, horsetail, pears, or celery root).

Recommendations for Pharmacologic Antiinflammatory Prophylaxis of Attacks of Acute Gout

The TFP recommended pharmacologic antiinflammatory prophylaxis for all case scenarios of gout where ULT was initiated, given high gout attack rate frequencies in early ULT (evidence A) (see Figure 5 in the original guideline document). For gout attack prophylaxis, the TFP recommended, as a first-line option, use of oral colchicine (evidence A). The TFP also recommended, as a first-line option (with a lower evidence grade than for colchicine), the use of low-dose NSAIDs (such as naproxen 250 mg orally twice a day), with proton-pump inhibitor therapy or other effective suppression therapy for peptic ulcer disease and its complications, where indicated (evidence C).

In their evaluation of colchicine evidence in gout attack prophylaxis, the TFP specifically recommended low-dose colchicine (0.5 mg or 0.6 mg orally once or twice a day, with dosing further adjusted downward for moderate to severe renal function impairment and potential drug–drug interactions) as appropriate for gout attack prophylaxis. The TFP did not vote on specific quantitative renal function impairment–adjusted dosing of oral colchicine. Since a pharmacokinetic analysis suggesting colchicine dose should be decreased by 50% below a creatinine clearance of 50 ml/minute is unpublished in peer-review form, specific quantitative colchicine dose adjustment in CKD is the decision of the treating clinician.

The TFP, in discussion without a specific vote, recognized the evidence that colchicine and low-dose NSAID prophylaxis fail to prevent all gout attacks in patient populations after initiation of ULT. As an alternative gout attack prophylaxis strategy in patients with intolerance or contraindication or refractoriness to both colchicine and NSAIDs, the TFP recommended use of low-dosage prednisone or prednisolone (defined here as ≤10 mg/day) (evidence C). Nevertheless, concerns were raised in discussion among the TFP and by the other authors regarding particularly sparse evidence for efficacy of this low-dose strategy. Given the known risks of prolonged use of corticosteroids, the authors urge clinicians to be particularly attentive in reevaluating the risk/benefit ratio of continued corticosteroid prophylaxis as the risk of acute gout attack decreases with time in conjunction with effective ULT. The TFP voted the use of high daily doses (i.e., >10 mg daily) of prednisone or prednisolone for gout attack prophylaxis to be as inappropriate in most case scenarios, and there was a lack of TFP consensus for more severe forms of chronic tophaceous gouty arthropathy. Last, there was a lack of TFP consensus on the risk/benefit ratio for off-label use of biologic IL-1 inhibition (evidence A) for antiinflammatory gout attack prophylaxis in patients who previously failed or had intolerance or contraindications to low doses of colchicine, NSAIDs, and prednisone or prednisolone for gout attack prophylaxis.

Duration of Antiinflammatory Prophylaxis of Acute Gout Attacks

The TFP recommended to continue pharmacologic gout attack prophylaxis if there is any clinical evidence of continuing gout disease activity (such as 1 or more tophi detected on physical examination, recent acute gout attacks, or chronic gouty arthritis), and/or the serum urate target has not yet been achieved. Specifically, the TFP voted to continue the prophylaxis for the greater of: 1) 6 months' duration (evidence A), 2) 3 months after achieving the target serum urate level for the patient without tophi detected on physical examination (evidence B), or 3) 6 months after achieving the target serum urate level, where there has been resolution of tophi previously detected on physical examination (evidence C) (see Figure 5 in the

original guideline document).

Definitions:

Levels of Evidence

Level A: Recommendations supported more than one randomized clinical trials or one or more meta-analyses

Level B: Recommendations derived from a single randomized trial or nonrandomized studies

Level C: Consensus opinion of experts, case studies, or standard of care

Clinical Algorithm(s)

The original guideline document provides clinical algorithms for:

- Overview of management of an acute gout attack
- Recommendations for the individual pharmacologic monotherapy options for an acute gouty arthritis attack
- Acute gouty arthritis attack management in the nothing by mouth (NPO) patient
- Pharmacologic antiinflammatory prophylaxis of gout attacks and its relationship to pharmacologic urate-lowering therapy (ULT)

Scope

Disease/Condition(s)

Acute gouty arthritis (gout)

Guideline Category

Counseling

Evaluation

Management

Prevention

Treatment

Clinical Specialty

Endocrinology

Family Practice

Internal Medicine

Nephrology

Rheumatology

Intended Users

Advanced Practice Nurses

Allied Health Personnel

Dietitians

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

- To develop nonpharmacologic and pharmacologic guidelines for treatments in gout that are safe and effective, i.e., with an acceptable risk/benefit ratio
- To provide guidelines useful for both rheumatologists and other health care providers on an international level
- To reflect best practice, supported either by level of evidence or consensus-based decision making

Target Population

Patients with gout

Interventions and Practices Considered

1. Treatment within 24 hours of an episode of acute gouty arthritis
2. Continuation of urate-lowering therapy during treatment for acute gouty arthritis
3. Patient education for self-management
4. Monotherapy
    - Oral nonsteroidal antiinflammatory drugs (NSAIDs)
    - Systemic corticosteroids
    - Colchicine
    - Cyclo-oxygenase (COX)-2 inhibitors for patients with contraindications to NSAID
    - Intraarticular steroid injections
5. Combination therapy
    - Intramuscular single-dose triamcinolone acetonide, followed by oral prednisone or prednisolone
    - Colchicine and NSAIDs
    - Oral corticosteroids and colchicine
    - Intraarticular corticosteroids with any of the other modalities
6. Management of inadequate response
7. Treatment of patients who are nothing by mouth (NPO)
    - Intraarticular corticosteroid injections
    - Intravenous or intramuscular methylprednisolone
    - Subcutaneous synthetic adrenocorticotropic hormone (ACTH)
8. Topical ice
9. Prophylactic therapy
10. Duration of antiinflammatory prophylaxis

Note: The Task Force Panel (TFP) considered the following but made no recommendation: intramuscular ketorolac, topical NSAIDs, intramuscular triamcinolone acetonide monotherapy. The TFP also considered complementary therapy with cherry juice or extract, salicylate-rich willow bark extract, ginger, flaxseed, charcoal, strawberries, black currant, burdock, sour cream, olive oil, horsetail, pears, or celery root and did not recommend them.

Major Outcomes Considered

- Effectiveness of treatment
- Improvement in pain scores

- Effectiveness of prevention strategies
- Frequency and severity of acute relapse
- Time to pain relief

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

PubMed and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched to find all articles on gout with the help of an experienced librarian. PubMed is a database of medical literature from the 1950s to present. CENTRAL includes references from PubMed, EMBASE, and the Cochrane Review Groups' specialized registers of controlled trials and hand search results. Search terminology (hedge) based on the Cochrane Highly Sensitive Search Strategy was used for identifying randomized trials. The hedge was expanded to include articles discussing research design, cohort, case–control, and cross-sectional studies. Limits added to the hedge include English language and the exclusion of "animal only" studies. The searches for all four domains were conducted simultaneously and therefore included terms for hyperuricemia and other gout-related issues.

The search of articles from 1995 to September 25, 2010 retrieved 5,830 articles from PubMed and CENTRAL. The review was divided into three stages: titles, abstracts from manuscripts, and entire manuscripts. At each stage, each title, abstract, or manuscript was included or excluded using prespecified rules (see the National Guideline Clearinghouse [NGC] summary of the ACR guideline 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia). Of the 5,830 titles, 192 duplicate titles and 82 non-English titles were excluded, with an additional 3,729 titles excluded based on exclusion criteria, leaving 1,827 titles, of which another 1,699 were excluded in the abstract phase. A total of 128 manuscripts remained that were further categorized into pharmacologic and nonpharmacologic studies.

Subsequently, the systematic review was updated by repeating the search with the same criteria to include any articles that were published between September 25, 2010 and March 31, 2011, and the guideline authors hand searched recent meeting abstracts from the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) for any randomized controlled trials that were yet to be published. The supplemental search resulted in four additional manuscripts and five meeting abstracts on pharmacologic agents, some of which were subsequently published and then reevaluated for evidence grade. Finally, there were 41 manuscripts on nonpharmacologic modalities (such as diet, alcohol, exercise, etc.) that included both retrospective and prospective studies, but all were excluded, since none were randomized controlled studies on interventions in gout patients. There were 87 manuscripts on pharmacologic agents for the treatment of patients with gout. Of these, 47 were randomized controlled trials and included in the evidence report, whereas the remaining 40 uncontrolled trials were excluded. A total of 21 manuscripts on urate-lowering therapy (ULT) were separately addressed (see the NGC summary of the ACR guideline 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia).

Number of Source Documents

A total of 30 manuscripts and 5 meeting abstracts were assessed, with 26 manuscripts and 2 meeting abstracts on acute gout and 4 manuscripts and 3 meeting abstracts on prophylaxis included in the evidence report and evaluated by the Task Force Panel.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Levels of Evidence

Level A: Recommendations supported more than one randomized clinical trials or one or more meta-analyses

Level B: Recommendations derived from a single randomized trial or nonrandomized studies

Level C: Consensus opinion of experts, case studies, or standard of care

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

The RAND/University of California-Los Angeles (UCLA) method requires 2 groups of experts: a core expert panel (CEP) that provides input into case scenario development, and a task force panel (TFP) that votes on the case scenarios. A systematic review of pertinent literature was performed concurrently, and a scientific evidence report was generated. This evidence report was then given to the TFP, in conjunction with a variety of clinical scenarios and clinical decision-making questions of interest for each scenario.

The level of evidence supporting each recommendation was ranked based on previous methods used by the American College of Cardiology and applied to other recent American College of Rheumatology (ACR) recommendations.

Methods Used to Formulate the Recommendations

Expert Consensus (Delphi)

Expert Consensus (Nominal Group Technique)

Description of Methods Used to Formulate the Recommendations

Design: RAND/University of California at Los Angeles (UCLA) Appropriateness Method Overview

The RAND/UCLA method of group consensus was developed in the 1980s, incorporates both Delphi and nominal group methods, and has been successfully used to develop other guidelines commissioned by the American College of Rheumatology (ACR). The purpose of this methodology is to reach a consensus among experts, with an understanding that published literature may not be adequate to provide sufficient evidence for day-to-day clinical decision making. The RAND/UCLA method requires two groups of experts: a core expert panel (CEP) that provides input into case scenario development, and a task force panel (TFP) that votes on the case scenarios. A systematic review of pertinent literature was performed concurrently, and a scientific evidence report was generated. This evidence report was then given to the TFP, in conjunction with a variety of clinical scenarios and clinical decision-making questions of interest for each scenario.

The diverse TFP, totaling 11 people, consisted of rheumatologists in a community private practice, a health maintenance organization practice, and a Veterans Affairs practice; a rheumatology physician–scientist inflammation researcher; a rheumatologist with expertise in clinical pharmacology; a rheumatologist gout expert that is an Internal Medicine Residency Director; a rheumatologist gout expert that is a Chair of Internal Medicine; two primary care internal medicine physicians; a nephrologist; and a patient representative.

There were two rounds of ratings, the first anonymous, with the members of the TFP instructed to rank each potential element of the guidelines on a risk/benefit Likert scale ranging from 1–9, followed by a face-to-face group discussion with revoting. A vote of 1–3 on the Likert scale was scored as *inappropriate*, where risks clearly outweigh the benefits; a vote of 4–6 was scored as *uncertain* ("lack of consensus"), where the risk/benefit ratio is uncertain; and a vote of 7–9 was scored as *appropriate*, where benefits clearly outweigh the risks. Case scenarios were

translated into recommendations, where the median voting scores were 7–9 on the Likert scale ("appropriate"), and if there was no significant disagreement, defined as no more than one-third of the TFP voting below the Likert scale level of 7 in the question. The final rating was done anonymously in a 2-day face-to-face meeting led by an experienced internal medicine physician moderator.

Case Scenarios

Through an interactive, iterative process, the CEP developed unique case scenarios of acute gouty attacks with varied treatment options, and the type of attack by severity, duration, and extent of the attack. The objective was to represent a broad spectrum of attacks that a clinician might see in a busy practice. For the case scenarios, the severity of acute gout differed based on self-reported worst pain on a 0–10 visual analog scale (VAS). Pain ≤4 was considered mild, 5–6 was considered moderate, and ≥7 was considered severe. Case scenarios also varied by duration of the acute gout attack; this was divided into early (<12 hours), well established (12–36 hours), and late (>36 hours). Case scenarios also varied in the number of active joints involved: 1 or a few small joints, 1 or 2 large joints (ankle, knee, wrist, elbow, hip, or shoulder), and polyarticular involvement (defined as either acute arthritis involving 3 separate large joints, or acute arthritis of 4 or more joints, with arthritis involving more than 1 "region" of joints). Joint regions were defined as: forefoot (metatarsal joints and toes), midfoot (tarsal joints), ankle/hindfoot, knee, hip, fingers, wrist, elbow, shoulder, or other (see Figure 1 in the original guideline document). The management strategies presented were developed for case scenarios involving gouty arthritis, but the intent was that acute bursal inflammation due to gout (e.g., in the prepatellar or olecranon bursa) and small joint involvement would have comparable recommendations for overall management strategies.

Developing Recommendations from Votes by the TFP

A priori recommendations were derived from only positive results (median Likert score ≥7). In the text below, all recommendations derived from TFP votes are denoted by an accompanying evidence grade. In addition to TFP vote results, the panel provided some statements based on discussion (not votes). Such statements are specifically described as discussion items (rather than TFP-voted recommendations) in the "Major Recommendations" field. The guideline authors also comment on specific circumstances where the TFP did not vote a particularly important clinical decision-making item as appropriate (i.e., the median Likert score was ≤6 or there was a wide dispersion of votes despite a median score of ≥7). Samples of voting scenarios and results are shown in Supplemental Figure 1 (available in the online version of the original guideline document at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658).

So that the voting panel could focus on gout treatment decisions, a number of key assumptions were made, as described in part 1 of the guidelines (see the National Guideline Clearinghouse [NGC] summary of the ACR guideline 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia). Importantly, each proposed recommendation assumed that correct diagnoses of gout and acute gouty arthritis attacks had been made for the voting scenario in question. For treatment purposes, it was also assumed that treating clinicians were competent, and considered underlying medical comorbidities (including diabetes mellitus, gastrointestinal disease, hypertension, and hepatic, cardiac, and renal disease) and potential drug toxicities and drug–drug interactions when making both treatment choices and dosing decisions on chosen pharmacologic interventions. The RAND/UCLA methodology used here emphasizes the level of evidence, safety, and quality of therapy, and excludes analyses of societal cost of health care.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published analyses were not reviewed.

Method of Guideline Validation

Peer Review

Description of Method of Guideline Validation

Peer Review of Recommendations

After the draft recommendations were submitted, the American College of Rheumatology (ACR) invited peer review, prior to journal review, done

by the ACR Practice Guidelines Subcommittee, the ACR Quality of Care Committee, and the ACR Board of Directors.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for most of the recommendations (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate therapy and antiinflammatory prophylaxis of acute gouty arthritis

Potential Harms

- Adverse effects of drugs used for gout treatment and prevention
- Drug-drug interactions for patients being treated for comorbidities
- Drug-disease interactions

Qualifying Statements

Qualifying Statements

- Guidelines and recommendations developed and/or endorsed by the American College of Rheumatology (ACR) are intended to provide guidance for particular patterns of practice and not to dictate the care of a particular patient. The ACR considers adherence to these guidelines and recommendations to be voluntary, with the ultimate determination regarding their application to be made by the physician in light of each patient's individual circumstances. Guidelines and recommendations are intended to promote beneficial or desirable outcomes but cannot guarantee any specific outcome. Guidelines and recommendations developed or endorsed by the ACR are subject to periodic revision as warranted by the evolution of medical knowledge, technology, and practice.
- Therapies that were approved after the original literature review, or diet and lifestyle measures studied after the original literature review, are not included in these recommendations.
- The ACR gout guidelines are designed to reflect best practice, supported either by level of evidence or consensus-based decision making. These guidelines cannot substitute for individualized direct assessment of the patient, coupled with clinical decision making by a competent health care practitioner. The motivation, financial circumstances, and preferences of the gout patient also need to be considered in clinical practice, and it is incumbent on the treating clinician to weigh the issues not addressed by this methodology, such as treatment costs, when making management decisions. Last, the guidelines for gout management presented herein were not designed to determine eligibility for health care cost coverage by third party payors.

Limitations of the Recommendations

- Limitations of the recommendations include that only approximately 30% were based on level A evidence, with approximately half based on level C evidence; this indicates the need for more studies in the aspects of gout management considered.
- The process used was limited by the current trial designs for assessment of acute gout therapies and prophylaxis of antiinflammatory pharmacologic agents in gout. For acute gout studies, most studies were on nonsteroidal antiinflammatory drugs (NSAIDs) and involved an active comparator and noninferiority trial design. However, the majority of these studies failed to provide a noninferiority margin, which needs to be defined a priori to assess the validity of these trials. Although the majority of studies assessed pain as the primary outcome for the acute gout trials, there is a lack of a single uniform measure that precludes meta-analysis.
- There is a lack of consensus on what time period after initiation of therapy constitutes a primary response, since trials ranged from a few

hours to 10 days.

- With the exception of recent analyses of biologic interleukin-1 (IL-1) inhibitors, there was a lack of robust clinical trials of gout attack prophylaxis using antiinflammatory pharmacologic agents. Also, the primary measure in these trials is the recurrence of self-reported acute gout attacks, an outcome that has not been validated using Outcome Measures in Rheumatology criteria. Efforts are underway to precisely define acute gout attack in gout clinical trials.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Clinical Algorithm

Foreign Language Translations

Patient Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Safety

Identifying Information and Availability

Bibliographic Source(s)

Khanna D, Khanna PP, Fitzgerald JD, Singh MK, Bae S, Neogi T, Pillinger MH, Merill J, Lee S, Prakash S, Kaldas M, Gogia M, Perez-Ruiz F, Taylor W, Liote F, Choi H, Singh JA, Dalbeth N, Kaplan S, Niyyar V, Jones D, Yarows SA, Roessler B, Kerr G, King C, Levy G, Furst DE, Edwards NL, Mandell B, Schumacher HR, Robbins M, Wenger N, Terkeltaub R. 2012 American College of Rheumatology guidelines for management of gout. Part 2: therapy and antiinflammatory prophylaxis of acute gouty arthritis. Arthritis Care Res (Hoboken). 2012

Oct;64(10):1447-61. [68 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2012 Oct

Guideline Developer(s)

American College of Rheumatology - Medical Specialty Society

Source(s) of Funding

Supported by a research grant from the American College of Rheumatology and by the National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH (grant K24-AR-063120).

Guideline Committee

Task Force Panel

Composition of Group That Authored the Guideline

Panel Members: Dinesh Khanna, MD, MSc, Puja P. Khanna, MD, MPH, Blake Roessler, MD: University of Michigan, Ann Arbor; John D. FitzGerald, MD, Sangmee Bae, MD, Shraddha Prakash, MD, Marian Kaldas, MD, Maneesh Gogia, MD, Daniel E. Furst, MD, Neil Wenger, MD: University of California, Los Angeles; Manjit K. Singh, MD: Rochester General Health System, Rochester, New York; Tuhina Neogi, MD, PhD, FRCPC, Hyon Choi, MD, DrPH: Boston University Medical Center, Boston, Massachusetts; Michael H. Pillinger, MD: VA Medical Center and New York University School of Medicine, New York; Joan Merill, MD: Oklahoma Medical Research Foundation, Oklahoma City; Susan Lee, MD, Robert Terkeltaub, MD: VA Healthcare System and University of California, San Diego; Fernando Perez-Ruiz, MD, PhD: Hospital Universitario Cruces, Vizcaya, Spain; Will Taylor, PhD, MBChB: University of Otago, Wellington, New Zealand; Frédéric Lioté, MD, PhD: Université Paris Diderot, Sorbonne Paris Cité, and Hôpital Lariboisière, Paris, France; Jasvinder A. Singh, MBBS, MPH: VA Medical Center and University of Alabama, Birmingham; Nicola Dalbeth, MD, FRACP: University of Auckland, Auckland, New Zealand; Sanford Kaplan, DDS: Oral and Maxillofacial Surgery, Beverly Hills, California; Vandana Niyyar, MD, Danielle Jones, MD, FACP: Emory University, Atlanta, Georgia; Steven A. Yarows, MD, FACP, FASH: IHA University of Michigan Health System, Chelsea; Gail Kerr, MD, FRCP(Edin): Veterans Affairs Medical Center, Washington, DC; Charles King, MD: North Mississippi Medical Center, Tupelo; Gerald Levy, MD, MBA: Southern California Permanente Medical Group, Downey; N. Lawrence Edwards, MD: University of Florida, Gainesville; Brian Mandell, MD, PhD: Cleveland Clinic, Cleveland, Ohio; H. Ralph Schumacher, MD: VA Medical Center and University of Pennsylvania, Philadelphia; Mark Robbins, MD, MPH: Harvard Vanguard Medical Associates/Atrius Health, Somerville, Massachusetts

Financial Disclosures/Conflicts of Interest

Managing Perceived Potential Conflict of Interest (COI)

Potential COI was managed in a prospective and structured manner. All of the participants intellectually involved in the project, whether authors or not, were required to fully disclose their relationships with any of the companies with a material interest in gout, listed in Supplemental Appendix A (available in the online version of the original guideline document at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658). Disclosures were identified at the start of the project and updated every 6 months. A summary listing of all perceived potential COI is available in Supplemental Appendix A (available in the online version of the original guideline document at

http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658). Based on the policies of the American College of Rheumatology (ACR), no more than 49% of the project participants were permitted to have COI at any given time, and a majority of the Task Force Panel (TFP) was required to have no perceived potential COI. It was further required that the project principal investigator (JDF) remain without perceived potential COI during the guideline development process, and for an additional 12 months afterward.

Dr. Dinesh Khanna has received consultant fees, speaking fees, and/or honoraria (less than $10,000 each) from Novartis and Ardea and (more than $10,000 each) from Takeda and Savient, and has served as a paid investment consultant for Guidepoint. Dr. Puja P. Khanna has received speaking fees (less than $10,000) from Novartis and (more than $10,000) from Takeda, and has served on the advisory board for Novartis. Dr. Pillinger has received speaking fees and/or honoraria (less than $10,000 each) from the RA Investigator Network, NY Downtown Hospital, Winthrop Hospital, and Einstein College of Medicine. Dr. Perez-Ruiz has received consultant fees, speaking fees, and/or honoraria (less than $10,000 each) from Novartis, Menarini, and Savient, and (more than $10,000) from Ardea. Dr. Lioté has received consultant fees, speaking fees, and/or honoraria (less than $10,000 each) from Novartis Global, Novartis France, and Ipsen, and has served as a paid investment consultant for Gerson Lehrman Group. Dr. Choi has served on the advisory boards (less than $10,000 each) for Takeda, URL, and Savient. Dr. Singh has received consultant fees, speaking fees, and/or honoraria (less than $10,000 each) from Ardea, Savient, Allergan, and Novartis, and (more than $10,000) from Takeda, and has received investigator-initiated grants from Takeda and Savient. Dr. Dalbeth has received consultant fees, speaking fees, and/or honoraria (less than $10,000 each) from Novartis, Takeda, and Ardea, has received research funding from Fonterra, and holds a patent from Fonterra for milk products for gout. Dr. Niyyar has received honoraria (less than $10,000) from the American Society of Nephrology. Dr. Kerr has served as a study investigator (more than $10,000 each) for Savient and Nuon. Dr. Edwards has received consultant fees, speaking fees, and/or honoraria (less than $10,000 each) from Savient, Takeda, Ardea, and Regeneron, and (more than $10,000) from Novartis, and has given expert testimony for Novartis. Dr. Mandell has received consultant fees, speaking fees, and/or honoraria (less than $10,000 each) from Savient, Novartis, and Pfizer. Dr. Schumacher has received consultant fees (less than $10,000 each) from Pfizer, Regeneron, West-Ward, and Ardea, and (more than $10,000) from Novartis. Dr. Terkeltaub has received consultant fees (less than $10,000 each) from Takeda, Savient, Ardea, BioCryst, URL, Regeneron, Pfizer, Metabolex, Nuon, Chugai, EnzymeRx, Ajanta, Anadys, Celgene, Isis, and Prescription Solutions, and (more than $10,000) from Novartis, has received grant support from the VA San Diego Healthcare System and the National Institutes of Health (NIH), and has served as a paid investment consultant for Leerink Swann, Medacorp, and Guidepoint.

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the American College of Rheumatology Web site .

Availability of Companion Documents

A supplemental figure and Appendix A are available from the Arthritis Care and Research Web site .

Patient Resources

The following are available:

- Gout. 2012 Sep. 5 p. Available in PDF in English and Spanish from the American College of Rheumatology (ACR) Web site.
- NSAIDs: nonsteroidal anti-inflammatory drugs. 2012 Aug. 5 p. Available in PDF from the ACR Web site .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original

guideline's content.

NGC Status

This NGC summary was completed by ECRI Institute on December 27, 2012. The information was verified by the guideline developer on January 17, 2013. This summary was updated by ECRI Institute on September 18, 2015 following the U.S. Food and Drug Administration advisory on non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs).

Copyright Statement

Disclaimer

NGC Disclaimer

The National Guideline Clearinghouseâ„¢ (NGC) does not develop, produce, approve, or endorse the guidelines represented on this site.

All guidelines summarized by NGC and hosted on our site are produced under the auspices of medical specialty societies, relevant professional associations, public or private organizations, other government agencies, health care organizations or plans, and similar entities.

Guidelines represented on the NGC Web site are submitted by guideline developers, and are screened solely to determine that they meet the NGC Inclusion Criteria which may be found at http://www.guideline.gov/about/inclusion-criteria.aspx.

NGC, AHRQ, and its contractor ECRI Institute make no warranties concerning the content or clinical efficacy or effectiveness of the clinical practice guidelines and related materials represented on this site. Moreover, the views and opinions of developers or authors of guidelines represented on this site do not necessarily state or reflect those of NGC, AHRQ, or its contractor ECRI Institute, and inclusion or hosting of guidelines in NGC may not be used for advertising or commercial endorsement purposes.

Readers with questions regarding guideline content are directed to contact the guideline developer.